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REVIEW

The Association Between Raised Coagulation Factor Levels and Venous Thrombo-embolism

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Introduction

The overall population incidence of venous thrombo-embolism (VTE) is approximately 0.1% per year and increases steeply with age.[1] The commonest presentation is lower limb deep vein thrombosis (DVT), complicated in a proportion of patients by symptomatic acute pulmonary embolism (PE). The latter remains the commonest single cause of potentially preventable death in surgical and obstetric patients. The commonest long-term complication of DVT is the post-thrombotic syndrome (PTS), which develops in up to 20% of cases, resulting in significant morbidity and enormous health care and socio-economic costs. Virchow's Triad describes the risk factors for VTE; namely, altered endothelium, blood flow and hyper-coagulability (thrombophilia [TP]).[2] TP may be acquired or inherited, and may affect the clotting and/or fibrinolytic cascades (Table 1, Fig. 1). The classical 'deficiency' TP, such as protein C and S and ATIII deficiency, can predispose to extensive and atypical episodes of VTE in early life; especially if more than one co-exists in the same patient along with other environmental factors. However, as the majority of patients affected by VTE do not apparently have a 'deficiency' TP, their contribution to the overall burden of VTE remains difficult to define.[3,4] Nevertheless, a significant proportion of DVT do develop in the absence of apparently significant environmental risk factors. This suggests that other, as yet incompletely defined, TP may contribute to these so-called 'idiopathic' cases by raising patients above their thrombotic threshold. Thus, in addition to the 'deficiency' TPs, a growing group of 'gain in function' TPs is being recognised. This review examines the evidence for the role of coagulation factors VIII, IX, and XI in VTE, and the implications of this new knowledge for clinical practice.

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Factor VIII

The relevant biology

Factor VIII (FVIII) is a vitamin-K dependent coagulation factor, which is primarily synthesised in the liver and circulates in plasma in a non-covalent complex with von Willebrand factor (vWF). Stimulation of coagulation cascade leads to the generation of a small amount of thrombin, which along with factor Xa, activates FVIII, resulting in its release from vWF. In the absence of vWF the half-life of FVIII and its plasma levels are greatly reduced.[5] Once activated, FVIIIa acts as a key co-factor in the FIXa-mediated conversion of FX to FXa. Inactivation of FVIIIa results from proteolytic cleavage by activated protein C (APC) or, as it is intrinsically unstable, by spontaneous dissociation. In haemophilia A, there is a congenital

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Table 1. Recognised thrombophilias and other risk factors for VTE

Inherited TP	Acquired TP	Environmental risk factors
Protein C (PC) deficiency	Antiphospholipid syndrome	Age
Protein S deficiency	Hyperhomocysteinaemia (HHcy)	Pregnancy and puerperium
Antithrombin deficiency	Resistance to activated PC	Prolonged surgery
Factor V Leiden	Dysfibrinogenaemia	Malignancy
PT 20210 mutation		Immobility
Hyperhomocysteinaemia (HHcy)		Hormone therapy

deficiency of FVIII resulting in a spontaneous haemorrhagic state. FVIII activity (FVIII:c) is measured by the ability to correct the elevated activated partial thromboplastin time (aPTT) of FVIII-deficient plasma. FVIII antigen (FVIII:Ag) is measured using a sandwich enzyme-linked immunosorbent assay (ELISA). In laboratories validated against international standards, the normal range is 50–150 IU/dl where 1 ml of pooled international standard plasma contains 1 unit of FVIII.

ABO blood group genes are the main determinants of vWF and thus as they are bound in plasma, effectively determine normal FVIII levels. Group O individuals have the lowest FVIII levels and AB the highest levels, with the other group being intermediate.[5,6] In the normal Caucasian population FVIII levels are, therefore, skewed towards the upper end of normal range. FVIII levels increase approximately 5% every 5–10 years independent of obesity, smoking and hormonal status.[7,8] Levels are also elevated in

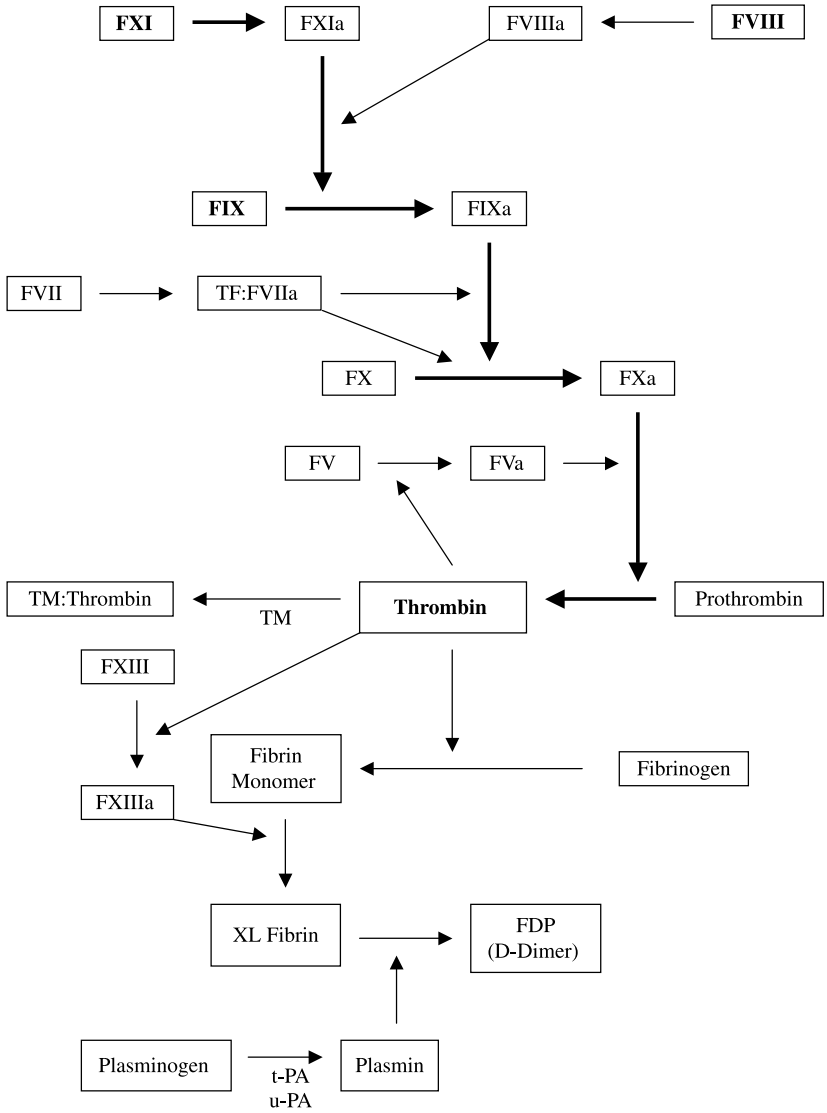

Fig. 1. An overview of the coagulation and fibrinolysis cascade (TF, tissue factor; TM, thrombomodulin; FDP, fibrin degradation products).

females and black ethnic groups.[6] Transient rises are seen after strenuous exercise and this may be secondary to the effect of adrenaline.[9] Acute inflammatory conditions will also result in a temporary elevation in plasma level as part of the acute phase reaction. Plasma FVIII levels are raised along with vWF in pregnancy, surgery, chronic inflammation, malignancy, liver disease, hyperthyroidism, intravascular haemolysis, renal disease,[5] hypertriglyceridaemia,[10] hyperinsulinaemia,[10] and in diabetes mellitus (by up to 18%).[8,10] This may be related to endothelial cell damage or high levels of insulin in association with insulin resistant.

What is the nature and strength of the relationship between FVIII and VTE?

The Leiden thrombophilia study (LETS) was the first to report an association between elevated plasma FVIII levels and VTE.[11] Raised plasma FVIII levels (above the 90th centile in control population) were found in 25% of unselected patients with their first objectively confirmed venous VTE event compared with 11% in healthy, age- and sex-matched controls. This significant difference was independent of ABO status. This association has been confirmed in two further independent studies.[12,13] On the basis of these data, it is estimated that each 10 IU/dl increase in FVIII plasma level is associated with a 17% increase in thrombotic risk, even if level remain within the 'normal range'. It is important to note that there is no cut-off value above which a patient can be considered to be FVIII 'positive'.

High FVIII levels are a risk factor for recurrent VTE although the strength of the association is less well established.[12,14,15] In the most recent prospective study,[15] patients with either 'idiopathic' VTE or thrombotic events secondary to recognised environmental events such as immobility and surgery were followed up with objective testing for recurrent episodes of VTE. In the 'idiopathic' group, there was an independent, dose-dependent relationship between FVIII levels and risk of recurrent disease, with rates of recurrent VTE rising from 7% in those with FVIII levels $<$25th centile (of this group), up to 23% of those with levels $>$90th centile. However, this was not found to be the case in those patients in whom there was an obvious precipitating event prior to the index event.

High VIII levels probably act synergistically with other TPs and risk factors such as the OCP. For example, one study found a markedly increased VTE risk in individuals with both high FVIII and factor V Leiden (FVL), compared with those with either TP in isolation.[16] In patients on the combined OCP elevated FVIII levels was shown to increase the thrombotic risk 10-fold compared to those with lower FVIII levels.[17]

What causes high FVIII levels?

High plasma FVIII levels can be regarded as both an inherited and/or acquired TP for VTE. Although the raised FVIII levels observed in patients with VTE was originally considered to reflect the acute phase response, subsequent work has shown that FVIII levels remain elevated long after the acute phase response has terminated and are independent of fibrinogen, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[18,19] It has also been suggested that elevated FVIII results from chronic endothelial cell (EC) stimulation but levels do not correlate with other EC markers such as soluble thrombomodulin (sTM), tissue plasminogen activator (tPA), and plasminogen activator inhibitor (PAI)-1.[20] A strong relationship exists between FVIII and vWF levels suggesting a genetic basis for high FVIII levels.[11,21,22] However, this relationship is imperfect, suggesting the presence of other genetic influences on FVIII levels related to putative, but as yet unsubstantiated, polymorphisms of the vWF FVIII binding domains, the vWF gene itself and the aPC cleavage sites.[12,23–25]

How do high FVIII levels result in VTE?

Elevated FVIII levels whether due to increased synthesis, enhanced stability or reduced inactivation, reduce the duration of the initiation phase of coagulation and thus increase the generation of thrombin.[22,26,27] Thus, patients with VTE and elevated FVIII have significantly higher levels of thrombin–antithrombin (TAT) complexes (TAT) and prothrombin (PF) fragments $1+2$ levels compared with patients with VTE and normal FVIII levels and normal healthy controls.[22] However, while there was a significant relationship between FVIII and thrombin generation when both groups of patients with VTE were analysed together, this was not the case when those patients with high FVIII were analysed alone. This suggests that, above a certain level, FVIII may no longer be a rate-limiting factor in thrombin generation. Alternatively, another, as yet unidentified, factor may be leading to high thrombin and FVIII levels in these patients. Whatever the mechanisms, it is clear is that high FVIII levels, even those that fall within the so-called 'normal range', are associated with a marked prothrombotic diathesis.

Factor IX

The relevant biology

Factor IX is also vitamin K-dependent coagulation factor which is synthesised in the liver. It is activated by either the tissue factor (TF): FVIIa complex or by FXIa, and in turn activates FX in the presence of FVIIIa and platelets, or phospholipid (Fig. 1). Haemophilia B (Christmas disease) is an X-linked recessive congenital deficiency of FIX, which leads to a haemorrhagic state that is clinically less severe than Haemophilia A. Plasma levels are measured in a similar manner to FVIII and the normal range is 50–150 IU/dl. Large epidemiological studies have shown that FIX levels are associated with a number of known risk factors for VTE; namely, age,[27,28] the oral contraceptive pill (OCP), hormone replacement therapy (HRT), menopause, body mass index, cholesterol, triglycerides, blood pressure, smoking, and low socio-economic grouping.[27–30]

What is the nature and strength of the relationship between FIX and VTE?

FIX level was found to be an independent risk factor for VTE in two recent case–control studies.[28,31] In the LETS study, patients with high plasma levels of FIX (above the 90th centile of that found in control population) had a two-fold increase in VTE risk. This risk was higher in women and, as with FVIII, significantly correlated with absolute levels.[28] High plasma FIX levels are also associated with recurrent VTE in patients with unprovoked primary events, with a similar dose-response effect. However, as with FVIII, the size of this risk is less clear as the small sample sizes inherent in these studies make multiple adjustments for confounding variables difficult.[32] High FIX levels also appear to interact with other known TPs and risk factors for VTE.[28,31] For example, the presence of high FVIII and FIX levels results in an eight-fold increase in VTE risk. Similar synergistic effects have been found with aPC resistance and ATIII deficiency, and the use of HRT.[31]

What causes high FIX levels?

There is currently insufficient evidence to determine whether high FIX levels have a genetic origin or simply reflect environmental effects on FIX levels. It is unlikely to be a result of an acute phase response as factor IX is not an important reactant in inflammation, and the VTE risk associated with high FIX is unaffected by CRP levels.[28]

How do high FIX levels result in VTE?

FIX levels are strongly associated with TAT and PF 1+2.[27] This appears to be due to TF-dependent and FX-independent, thrombin generation. The fact that FIX activation is dependent upon FVIII may explain their synergistic effect on VTE risk.[29]

Factor XI

The relevant biology

Factor XI circulates in complex with high molecular weight kininogen (HMWK) and is then activated. The most likely mechanisms of FXI activation *in vivo* is by low levels thrombin on the surface of activated platelets. FXI acts through a feedback effect on FIX and FVIII, which results in high levels of thrombin, and thus in turn leads to increased levels of thrombin activated fibrinolysis inhibitor (TAFI) and thus inhibition of fibrinolysis. Inherited factor XI deficiency, due to genetic mutations on chromosome 4, results in a moderate bleeding disorder most commonly seen in Ashkenazi Jews and only sporadically in non-Jewish populations. Tissues such as the oropharynx and the urinary tract where there are high levels of local fibrinolytic activity are primarily affected.[33] There are several circulating protease inhibitors of FXIa and binding to platelets may partially protect it from degradation.

What is the nature and strength of the relationship between FXI and VTE?

The association between high FXI levels and VTE has only been determined very recently. In the LETS study, patients with FXI levels >90th centile (of control population) had a doubling of VTE risk that was unaffected by sex, age, OCP and known genetic TPs.[34] Further studies are awaited to confirm this relationship with VTE, and determine the relationship with recurrent VTE and other known TPs as well as the origin of elevated FXI levels.

Conclusion

It seems increasingly likely that the majority of patients developing VTE have an inherited and/or

acquired underlying abnormality of their coagulation and/or fibrinolytic systems, in addition to the well-recognised environmental risk factors such as surgery and immobilisation. Specifically, there is growing evidence of a causal association between FVIII, FIX and, to a lesser extent FXI, levels and VTE, even when levels are within the so-called 'normal range'. This additional risk has to be viewed in the light of the overall clinical context and can be expressed in relative or, more perhaps usefully when dealing with individual patients as opposed to populations, absolute terms. The contribution that a particular TP makes to the overall community burden of VTE (the attributable risk) depends upon its thrombotic power (relative risk) and the number of affected individuals (prevalence). Although the 'gain in function' TPs, such as raised factor levels and hyperhomocysteinaemia (HHcy), may be 'less powerful' that some of the classical 'deficiency' TPs, their overall attributable risk is likely to be far greater because they are much more common.[21]

How should this new information impact upon everyday clinical practice? In the majority of patients, without a personal of family history of VTE, or another known TP, routine full TP screen including measurement of factor levels is probably not indicated prior to environmental exposure of VTE risk; for example, surgery. However, in patients who do exhibit one of more of those pre-existing risk factors, knowledge of the factor levels before and perhaps after surgery may impact upon the nature and duration of VTE prophylaxis. For example, a surgeon may wish to continue low molecular weight heparin VTE prophylaxis post-discharge until factor levels return to normal (or pre-operative) levels in a patient with a previous VTE episode undergoing a femoro-distal bypass. In addition in patients with multiple TP, it is vital that this is included in the pre-operative consent process as the greatly increased risk of VTE, even with prophylaxis may outweigh any benefit of the procedure. Although this paper has specifically discussed VTE, it is worth re-emphasising that some TP, including raised factor levels, may also predispose to arterial thrombosis of both native vessels and autogenous and prosthetic conduits.[35]

In the absence of a major environmental VTE stimulus such as surgery, it is generally agreed that the risks of anticoagulation with warfarin probably outweigh the benefits in patients with isolated raised factor levels.[32] However, in those with other known TPs, anticoagulation might be justified on a case-by-case basis, especially as safer anticoagulants such ximelagatran[36] enter the market. For this reason, we would recommend that, in both surgical and non-surgical patients deemed to be at high risk of VTE, factor levels be included within the standard TP screen.

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